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Vascular Mediators in Chronic Lung Disease of Infancy: Role of Endothelial Monocyte Activating Polypeptide II (EMAP II)

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Abstract

Bronchopulmonary dysplasia (BPD) is a chronic lung disease of prematurity. Over the years, the BPD phenotype has evolved, but despite various advances in neonatal management approaches, the reduction in the BPD burden is minimal. With the advent of surfactant, glucocorticoids, and new ventilation strategies, BPD has evolved from a disease of structural injury into a new BPD, marked by an arrest in alveolar growth in the lungs of extremely premature infants. This deficient alveolar growth has been associated with a diminution of pulmonary vasculature. Several investigators have described the epithelial/vascular co-dependency and the significant role of crosstalk between vessel formation, alveologenesis, and lung dysplasia's; hence identification and study of factors that regulate pulmonary vascular emergence and inflammation has become crucial in devising effective therapeutic approaches for this debilitating condition. The potent antiangiogenic and proinflammatory protein Endothelial Monocyte Activating Polypeptide II (EMAP II) has been described as a mediator of pulmonary vascular and alveolar formation and its expression is inversely related to the periods of vascularization and alveolarization in the developing lung. Hence the study of EMAP II could play a vital role in studying and devising appropriate therapeutics for diseases of aberrant lung development, such as BPD. Herein, we review the vascular contribution to lung development and the implications that vascular mediators such as EMAP II have in distal lung formation during the vulnerable stage of alveolar genesis.

Keywords

AIMP1; SCYE1; bronchopulmonary dysplasia; prematurity

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Introduction

LUNG MORPHOGENESIS AND PULMONARY ENDOTHELIUM: THE CROSS-TALK

The human vascular network is composed of two major circulations, systemic and pulmonary, connected in series and separated by the heart. Blood vessel formation is a process that is highly regulated, involving not only proliferation and differentiation of the vasculature, but also regression and stasis of these structures (Scavo et al., 1998). Hence, these processes warrant a delicate balance between the proangiogenic and antiangiogenic factors. Two identified and distinct processes; vasculogenesis and angiogenesis are responsible for the majority of vascularization during fetal growth and development (Poole and Coffin, 1989; Coffin et al., 1991). First, vasculogenesis is the formation and organization of angioblasts into linear aggregates that form primitive capillary plexus during embryogenesis before the formation of vascular structures. Second, angiogenesis is the extension of previously formed vessels into undervascularized regions where differentiated endothelial cells proliferate, sprout from previously formed vessels, and form new vascular structures (Jeffery and Reid, 1973; Burri et al., 1974; Kauffman, 1981). Defects in endothelial cell development and vessel formation and function lead to embryonic lethality and are important in the pathogenesis of vascular diseases (Park et al., 2013).

The pulmonary circulation is a highly specialized vascular bed that physically and functionally connects the heart and the lungs (Peng and Morrisey, 2013). Its formation involves a complex, multistep process that includes formation of primitive vascular networks; remodeling with local regression and branching and then specialization toward larger vessels like arteries, veins, and lymphatics (deMello et al., 1997; Galambos and deMello, 2007). A multitude of growth factors play a role in these processes, interaction of which leads to various budding and branching events that generate a tree like system of capillaries and epithelium, which forms the mature lung organ capable of air exchange at the alveolar endothelial cell interface (Copland and Post, 2004; Cardoso and Lu, 2006; Maeda et al., 2007; Millien et al., 2008; Schwarz and Cleaver, 2009). The chronological stages of lung development based on growth of specific pulmonary vasculature and epithelial structures are consistent across all mammalian species (Ten Have-Opbroek, 1981; Kimura and Deutsch, 2007). There are five phases of structural lung development that occur at progressive times during gestation, namely embryonic, pseudoglandular, canalicular, saccular, and alveolar stages (Loosli and Potter, 1959). The timing of the phases is approximate, with overlap between the various stages and variation among different fetuses (Zeltner and Burri, 1987). The highly proliferative and vascular canalicular stage occurs between the 16th and 27th weeks of gestation. The terminal sac formation, or the saccular stage encompasses the period from 28 to 36 weeks, after which the alveolar stage starts. The canalicular and saccular stages are the most vulnerable periods in lung development; any aberration during these stages could possible result in an arrest of alveolar development leading to lung dysplasias such as bronchopulmonary dysplasia (BPD) (Baraldi and Filippone, 2007). Using different ablative strategies to eliminate the lung vasculature, both in vivo and in lung explants, it has been shown that the proximity of the vasculature is essential for distal alveolar formation and patterning airway branching (Schwarz et al., 2004).

Increasing evidence suggests that blood vessels actively promote alveolar growth during lung development and contribute to the maintenance of alveolar structures (Thebaud and Abman, 2007; Schwarz et al., 2009; Ding et al., 2011). Within the complex emerging vascular network, proangiogenic vascular endothelial growth factor (VEGF) and its receptors, VEGFR1 and VEGFR2, are essential for vascular development and embryonic survival (Carmeliet et al., 1996a, 1996b), as modulators of endothelial differentiation, blood vessel formation, and morphogenesis (Ferrara et al., 2003). At a mechanistic level, epithelial expressed VEGF prompts endothelial cells to move toward the epithelium where arrival of the endothelium to the epithelial interface coincides with epithelial differentiation during the proliferative, canalicular stage (Schwarz et al., 2009). In addition to being a master regulator of blood vessel formation, VEGFR2 has been demonstrated to directly promote the expansion of the lymphatic network and further define the molecular mechanisms controlling development of the lymphatic vascular system (Dellinger et al., 2013). Factors controlling the transcriptional regulation of VEGF and VEGFR mediate distal alveolar development. For example, using chromatin precipitation, NF-κB was found to be a direct regulator of VEGFR2 transcription. Blockade of NF-κB induced a reduction in neonatal pulmonary vasculature and was associated with alveolar simplification (Iosef et al., 2012). Hypoxia-inducible factors (HIFs), oxygen responsive transcription factors that influence VEGF and VEGF receptor expression influence alveolar formation. A recent study suggests that prenatal hypoxia insults, at least in late gestation, influence pulmonary VEGF and VEGF receptor expression through the down-regulation of HIF pathways and impair fetal lung growth and maturation (Tsao and Wei, 2013). Identification of those factors such as HIF that promote normal alveolar development may be useful targets for alveolar regeneration (Vadivel et al., 2013).

Not all growth factors that influence endothelial cells specifically target only the endothelium. In contrast to vascular growth factors, proteins previously identified as vascular markers have recently been shown to extend their influence beyond endothelial cell boundaries. For example, Ephrin-B2, a tyrosine kinase ligand is involved in angiogenesis and is defined as a marker of endothelial arterial fate specification. EphrinB2 is necessary for normal alveolar development and exerts therapeutic benefit in protecting the lung from O_2-induced alveolar injury and pulmonary hypertension (Vadivel et al., 2012). Bennett et al. determined that the ephrin-B2 ligand found on primitive arterial vessels, also governed alveolar growth and mechanics beyond the confines of the endothelium as ephrin-B2 reverse signaling also mediated distal alveolar formation, alveolar fibrillogenesis (the deposition of fibronectin in the distal alveoli), and pulmonary compliance (Bennett et al., 2013). Further supporting a more extensive role of endothelial selective factors in pulmonary morphogenesis was demonstrated by the mutation of the vascular tone mediator of smooth muscle contraction endothelial nitric oxide synthetase, where transgenic mice resulted in capillary hypoperfusion, misaligned pulmonary veins, and a paucity of distal alveolar branches were identified (Han et al., 2004).

Of interest, the lung phenotype of endothelial nitric oxide synthase mutants closely resembles alveolar capillary dysplasia in humans, where a universally fatal form of persistent pulmonary hypertension of the newborn, presents with defective lung vascular

development and respiratory distress in newborn (Han and Stewart, 2006). However, an alternative consideration is that disturbances in the vascular mediators ephrin-B2 and endothelial nitric oxide synthase disrupted the vasculature that itself was necessary for other aspects of alveolar development. Therefore, vascular growth factors have been described to work in a very complex and coordinated manner through various pathways to form the pulmonary vasculature, which is critical in alveologenesis and gas exchange. A reduction in vascular growth factors, their receptors, or their enhanced degradation can lead to aberrant lung development and disease states. One such debilitating disease is BPD in which an arrest in pulmonary capillary formation possibly precedes severe alveolar dysplasia in premature infants.

ROLE OF ANTIANGIOGENIC PROTEIN: EMAP II IN PULMONARY MORPHOGENESIS

In contrast to the positive roles of angiogenic factors and their receptors, the inhibitory vascular factors provide a counterbalance to vessel formation during lung development. One such potent antiangiogenic factor, Endothelial Monocyte Activating Polypeptide II (EMAP II), plays a significant role in pulmonary vascular development and has been shown to inhibit lung neovascularization and airway epithelial morphogenesis (Schwarz et al., 2000a). First described as a pro inflammatory mediator (Kao et al., 1992, 1994), EMAP II was later determined to have significant antiangiogenic properties. EMAP II is a cytokine-like molecule first identified from murine methylcholanthrene A-induced fibrosarcomas (Kao et al., 1992) and is synthesized as a 34 kDa pro-form (pro-EMAP II), which is cleaved to the 22 kDa mature form. The mature form is responsible for most of its described biological activities (Kao et al., 1994). Schwarz et al. found that, pro-EMAP II resides on the cell membrane where within a proteinase sensitive 44 amino acid residue region, the enzyme cathepsin L cleaves pro-EMAP II to within 4 amino acids of the determined N-terminal sequence (Zhang and Schwarz, 2002; Liu and Schwarz, 2006). Mechanistically, examination of tumors treated with EMAP II suggested that EMAP II targeted endothelial cell viability as Schwarz et al. demonstrated that EMAP II induced endothelial cell apoptosis, inhibited tumor vessel formation, and suppressed primary and metastatic tumor growth (Schwarz et al., 1999a; Berger et al., 2000). Its antiangiogenic potential was further established when EMAP II was found to retard local tumor growth, significantly reduce microvessel counts, and induce a higher vascular thrombosis rate. Importantly, it was in these studies that EMAP II was recognized for its impact on nonendothelial cells, as there was also an associated reduction tumor cell proliferation (Schwarz and Schwarz, 2004). In addition to tumor vascular regulation, administration of EMAP II markedly diminished levels of herpes simplex virus-induced angiogenesis thereby reducing the severity of ocular stromal keratitis lesions (Zheng et al., 2001). These studies suggest that EMAP II is an angiostatic mediator that suppresses neovascularization.

In lung morphogenesis, where cell proliferation, neo-vascularization, and epithelial cell differentiation are the main emphasis, EMAP II plays an important role as a modulator of vascular and alveolar morphogenesis. Initial studies of murine pulmonary morphogenesis identified EMAP II's protein and mRNA to have an inverse correlation between expression and lung vascularization (Schwarz et al., 1999b). For example, during the embryonic and early pseudoglandular stages of lung development, EMAP II expression is high while the

vasculature is immature. In contrast, as the distal alveolar structure enters the proliferative canalicular stage, EMAP II expression abruptly falls and remains low through postnatal lung development with a transient surge of EMAP II protein expression during postnatal days 8 to 16 corresponding with the microvascular maturation of the lung. Importantly, early EMAP II protein and mRNA expression localizes to the epithelial interface with the foregut splanchnopleuric mesoderm at a time when expression of the classic early vascular markers are not found in that region. During the later vascular stages, EMAP II localizes to the perivascular regions of larger vessels suggesting a static role in vessel homeostasis (Schwarz et al., 1999b). These findings suggested a significant role for EMAP II in vascular formation during pulmonary morphogenesis.

Development of the pulmonary vascular and epithelial interface requires communication and interaction between the cellular components to form a function air-exchanging unit. Increasing evidence suggests that the vasculature has a critical role in modulating epithelial growth. The epithelial lining located deep in the distal airways, is vital to gas exchange. Alveolar formation in these distal parts of the lung involves transdifferentiation of alveolar type II and alveolar type I cells in direct conjunction with the endothelial cells. EMAP II's temporo-spatial location in this region suggested a role in distal alveolar formation. Although targeted ablation of EMAP II in the pulmonary vasculature would specifically address this issue, a targeted knockout mouse was not available. Therefore, an allograft model of distal lung development and neovascularization that avoided the placental barrier was used to determine the impact of EMAP II in lung development (Schwarz et al., 2000b). Delivery of exogenous EMAP II during the late pseudoglandular through saccular stages of lung development not only inhibited neovascularization, but markedly altered lung morphogenesis including a lack of alveolar type I and II cells and the induction of apoptosis. In contrast, delivery of an EMAP II function antibody marked increased vessel density and the expression of the alveolar type II cell marker surfactant protein (Schwarz et al., 2000a). These studies suggested that the vascular mediator EMAP II had a role that extends beyond the endothelial cell. In vitro studies defined the interdependence of the epithelial–mesenchymal interactions and vasculature. Administration of the known vascular inhibitor EMAP II to a proxy of alveolar architectural formation, epithelial cyst formation, disrupted the organization of epithelial and mesenchymal cells into epithelial cystic structures, inhibited vascular development, and induced epithelial apoptosis. Conversely, epithelial cyst formation was facilitated by an EMAP II-blocking antibody (Schwarz et al., 2004). Although these studies established a link between the antiangiogenic growth factor EMAP II and epithelial cell survival, the impact EMAP II had on distal alveolar structural organization epithelial differentiation was unclear. A three-dimensional model of fetal lung self-assembly was used to better define the impact that EMAP II had on alveolar organization. Schwarz et al. (2011) discovered that dissociated fetal lung in the pseudoglandular stage had the innate ability to self-assemble into a three-dimensional lung formation that mimics structure, polarity, vasculature, and extracellular matrix expression. This three-dimensional lung formation, pulmonary body, afforded the ability to identify the role that EMAP II had on cell-intrinsic properties that that guide the lungs structural organization during morphogenesis by examining epithelial endodermal and mesenchymal mesodermal cell interactions (Schwarz et al., 2011). From these studies, it was determined

that in lung cellular interactions, EMAP II was able to influence cell–cell interactions by increasing the rate of pulmonary body self-assembly while decreasing overall cell–cell cohesion. Of interest, EMAP II cohesion effects were exclusively targeted to the mesenchymal cell population where it interfered with the mesenchymal cells production of the extracellular matrix protein fibronectin. However, the loss of fibronectin deposition and altered mesenchymal cell–cell interactions was also associated with an inhibition of epithelial cell polarity and surfactant protein C expression. These studies supported the role of EMAP II on both mesenchymal and epithelial cell populations in lung structural and morphologic development through different molecular mechanisms. Furthermore, these findings suggest that lung development may be influenced by the expression and function of antiangiogenic proteins through an adhesion-based mechanism with extracellular matrix (ECM) -facilitated signaling being a mediator of cell viability and differentiation (Schwarz et al., 2011). This concept that EMAP II targeted epithelial cell transdifferentiation through an ECM-facilitated signaling was further supported by its ability to disrupt in vitro alveolar type II → alveolar type I cell transdifferentiation. Taken together these studies support EMAP II's role as a regulator of distal alveolar structural development that can influence the formation of essential and functional gas-exchanging units (Chen et al., 2012).

The observation in in vivo and in vitro models that EMAP II targeted ECM deposition, endothelial cell viability, and epithelial cell transdifferentiation suggested that a subset of cells engaged in activities that are dependent on cell adhesion and migration were being targeted. Mechanistically, excess EMAP II was found to inhibit endothelial cell adhesion to fibronectin (FN), disrupt actin stress fibers and disassemble cellular fibronectin matrices. Furthermore, EMAP II's ability to disrupt cellular adhesion to FN was due to its direct interaction with integrin alpha5 beta1 in an RGD dependent manner (Schwarz et al., 2005). In addition to FN being essential for endothelial cell viability and adhesion, recent studies suggest that progression of epithelialization is dependent on FN deposition at epithelial–mesenchymal interface (Koshida et al., 2005; Larsen et al., 2006; Julich et al., 2009). Taken together, EMAP II's disruption of developing lung fibronectin deposition may interfere with distal epithelial transdifferentiation, vessel formation, and sturctural organization.

In contrast to matrix driven mechanisms, alteration in expression levels of VEGFA have been shown to markedly influence distal lung dysplasia (Tsao and Wei, 2013). Awasthi et al. showed that EMAP II binds to the VEGFR1 and VEGFR2 receptors preventing them from interacting with their VEGFA ligand. Furthermore, EMAP II markedly reduces VEGFA signaling and phosphorylation of VEGFR1 and VEGFR2 resulting in the inhibition of VEGFA mediated endothelial cell proliferation and migration (Awasthi et al., 2009). Of interest, HIF-1 alpha, a transcriptional regulator of VEGFA is influenced by EMAP II. Recent studies show that EMAP II modulates endothelial cell responses by proteolytic degradation of HIF-1 alpha (Tandle et al., 2009) and interfering with VEGF induced proangiogenic signaling (Awasthi et al., 2009). EMAP II's targeted disruption of VEGFA transcription and signaling and interference of endothelial cell adhesion may contribute to the pathogenesis of lung dysmorphogenesis such as BPD.

In the first ever consideration of the hypothesis that EMAP II expression contributed to distal alveolar dysmorphogenesis in premature infants, Quintos-Alagheband et al. had found

EMAP II expression to be profoundly elevated in autopsy lung samples of human infants with BPD. Tissue obtained from human neonates with pathologic signs of BPD had a marked diffuse increase in EMAP II expression in the alveolar region on immunohistochemistry (Quintos-Alagheband et al., 2004). In contrast, age-matched control infants had minimal expression of EMAP II in this region. Consistent with these findings, EMAP II levels were significantly elevated in the perivascular stroma and lung periphery in the neonatal baboon model of BPD (Quintos-Alagheband et al., 2004). In this model, gestation-matched controls were compared with premature baboons treated in a baboon intensive care unit with oxygen as needed. In situ hybridization determined that at baseline EMAP II mRNA at 125 days (canalicular stage) is expressed throughout the subepithelium of the bronchi and diffusely in the distal alveolar regions whereas its expression in the perivascular areas was minimal. By the beginning of the saccular stage, i.e., 140 days, there was a slight increase in its perivascular expression, but a decrease in its overall lung expression. By term gestation, i.e., 160 and 175 days EMAP II expression was predominantly in the perivascular area and minimal in the alveoli. In contrast to its normal decline between days 125 and 160; in the preterm baboon model of BPD, EMAP II abundance was markedly elevated. EMAP II expression was prematurely accelerated in a perivascular distribution and was associated with the dysplastic undervascularized alveolar regions of the distal lung consistent with the BPD phenotype. These studies support a strong link between BPD and EMAP II expression. The authors speculated that premature birth exposes infants to factors which directly or indirectly upregulate EMAP II which then negatively influences neovascularization leading to disrupted alveolarization.

EMAP II AND INFLAMMATION

In addition to the role of EMAP II in altering the physiology of angiogenesis, it has been described to have transient inflammatory properties (Kao et al., 1992, 1994; Mueller et al., 2003; Murray et al., 2004, van Horssen et al., 2006a, 2006b; Journeay, Janardhan et al., 2007; van Horssen et al., 2008). These include the chemotactic effects toward monocytes and granulocytes, and direction of leukocyte migration involving an increase in intracellular calcium (Kao et al., 1992, 1994). Van Horssen et al. found that EMAP II sensitizes endothelial cells to apoptosis by facilitating tumor necrosis factor (TNF) -R1 apoptotic signaling by means of TNF-R1-Associated Death Domain (TRADD) mobilization and introduce a molecular and antiangiogenic explanation for the TNF sensitizing properties of EMAP II in tumors (van Horssen et al., 2006b). It also up regulates production of inflammatory molecules like TNF, and interleukin-8 in mononuclear phagocytes and polymorph nuclear leukocytes and promotes adhesion of monocytes. (Kao et al., 1992, 1994; Ko et al., 2001; Park et al., 2002). Murray et al. found that EMAP II causes a dose-dependent inhibition of proliferation and apoptosis in Jurkat T lymphocytes and mitogen-activated peripheral blood mononuclear cells and constitutes a component of a novel, immunosuppressive pathway in solid tumors (Murray et al., 2004). Later the same authors linked EMAP II ability to induce lymphocyte death with hypoxia in colorectal cancer (Youssef et al., 2006). Lipopolysacchride causes lung inflammation, and induces rapid EMAP II expression in lungs and in models of acute lung injury (Journeay et al., 2007). In addition, intratracheal instillation of EMAP II results in monocyte, macrophage and granulocyte recruitment without altering the lung expression of interleukin-1β or MIP-2

(Journeay et al., 2007). interleukin-1β has been described to be critical in the early phase of acute lung inflammation while MIP-2 promotes recruitment of monocytes and granulocytes and hence these experiments point toward a direct proinflammatory role of EMAP II on the lungs. Proinflammatory environment in the perinatal period, secondary to chorioamnioitis (Watterberg et al., 1996), ureaplasma infection (Schelonka et al., 2005), and postnatal sepsis (Stoll et al., 2002), have all been associated with the development of BPD in preterm infants. Moreover, hyperoxia, a potent inflammatory stimulus has been well described in the pathogenesis of BPD (Bhandari, 2010). Hence the above-mentioned inflammatory properties, in addition to its angiostatic attributes, make EMAP II very relevant cytokine in the pathogenesis of chronic lung diseases including emphysema and BPD.

POSSIBLE ROLE OF EMAP II IN CHRONIC LUNG DISEASE OF INFANCY

Over the years, the definition of BPD has evolved. In 1967, BPD was described by Northway et al, as severe cystic lung injury resulting from mechanical ventilation and oxygen exposure (Northway et al., 1967) whereas in this era BPD is characterized by alveolar simplification and restrictive lung physiology, as a result of arrest of alveolar development and inflammation (Northway et al., 1967; Coalson, 1997; Kinsella et al., 2006). Despite numerous efforts, it still lacks effective treatment. Therefore, it is crucial to gain a better understanding on how alveoli and the underlying capillary network develop and how these mechanisms are disrupted in BPD. Studies indicate that the expression and signaling of the prominent angiogenic growth factor VEGF is impaired in BPD, contributing to the marked pulmonary vascular disease (Abman, 2010). Furthermore, infants that die with BPD have a marked reduction in VEGF and VEGFRs (Bhatt et al., 2001) making rescue of angiogenic signaling a critical component in BPD therapeutic approach (Thebaud et al., 2005). Exogenous VEGF protects against O2-induced arrested alveolarization and stimulates lung vascular growth, but this results in immature and leaky vessels (Kasahara et al., 2000; Thebaud et al., 2005). Hence the exact pathophysiological role of VEGF in neonatal respiratory failure is not yet entirely clear. Current animal and human studies exhibit controversial results. Though animal models are invaluable tools in the study of human lung disease, multitude of differences in physiology make the findings less translatable to humans. Rightly, Bhandari has highlighted the importance of studying the temporal relationship of VEGF and lung development in human neonates and developmentally appropriate models with BPD (Meller and Bhandari, 2012). Also, a need arises to look at the contribution of other modulators of impaired vascular development and inflammation in this chronic lung dysplasia. EMAP II is one such suitable candidate, as its untimely overexpression could cause alveolar dysplasia secondary to its antiangiogenic and proinflammatory properties (Fig. 1). Furthermore, excess EMAP II inhibits VEGF ligand mediated signaling through the VEGFR1/2 receptors, interferes with endothelial cell adhesion resulting in apoptosis, and interferes with ECM deposition. These factors have all been found to directly contribute to lung dysplasia. Taken in conjunction with EMAP II's ability to interrupt distal alveolar formation, induce lung dysplasia, interfere with alveolar type II $\rightarrow$ type I cell transdifferentiation, and impede cell–cell cohesion of pulmonary mesenchymal cells we believe that the excess EMAP II expressed in the lungs of premature infants directly contributes to the formation of distal alveolar dysplasia known as BPD.

EMAP II IN CHRONIC LUNG DISEASE OF ADULTS

Recent studies determined that EMAP II has a role in adult lung diseases where it has been recognized as a possible biomarker and modulator of cigarette smoke induced chronic obstructive pulmonary disease (COPD). Chronic lung disease of infancy and chronic lung disease of adulthood bear both pathological and clinical resemblances and a recent report suggests that infants with mild BPD have potential of developing COPD in adulthood owing to the similar impairments in respiratory mechanics and lung structure (Brostrom et al., 2010). Moreover a potential link between COPD and BPD has been highlighted in various recent editorials (Filippone et al., 2010). Clauss et al. found that the EMAP II levels were elevated in the bronchoalveolar lavage of both current and ex-smokers and linked EMAP II to the pathogenesis of COPD. In murine models, they showed that EMAP II levels were increased in cigarette smoke induced emphysema. They conducted lung specific overexpression of EMAP II in transgenic mice that induced emphysema like changes (Clauss et al., 2011). In these experiments the mechanism of EMAP II up regulation involved an apoptosis-dependent feed forward loop, because caspase-3 instillation in the lung markedly increased EMAP II expression, while caspase inhibition decreased its production, even in transgenic EMAP II mice. Through this study, the authors suggested that EMAP II perpetuated the mechanism of lung emphysema in mice and is a suitable target for neutralization treatment. These findings raise further questions about the possible role of EMAP II in other chronic lung diseases such as BPD that has a very similar phenotype to emphysema.

In conclusion, it is clear that the vasculature plays an important role in normal lung development. Aberrations in normal pulmonary vascular development are involved in debilitating lung dysplasia's like BPD. We speculate that EMAP II plays an important role in these processes and our current studies are further exploring the contribution that antiangiogenic proteins like EMAP II have in the pathogenesis of BPD.

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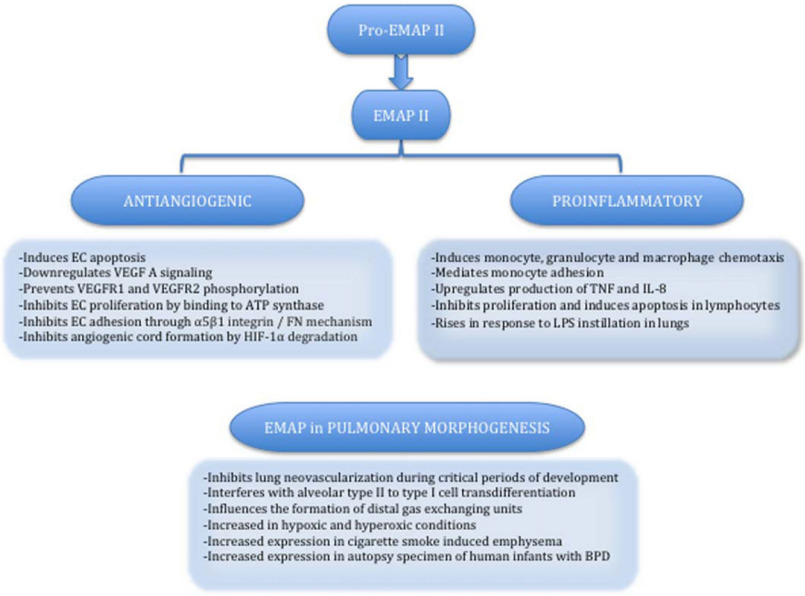

FIGURE 1.

EMAP II's antiangiogenic and pro-inflammatory properties may contribute to the pathologic processes associated with bronchopulmonary dysplasia.